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Synthesis of new organic analytical reagents

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Synthesis of new organic analytical reagents

Abstract

The investigation of the preparation of three organic compounds, 2,2-bipyrimidyl, 1,4-bis-(cyclohexoxy)-2,3-butanedionedioxime, and 2,2-thenilodioxime, analogs of useful analytical reagents in the specific or selective separation and/or determination of divalent metal ions has been carried out.

Disciplines

Chemistry | Organic Chemistry

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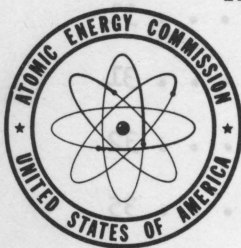
ISC-91

SYNTHESIS OF NEW ORGANIC ANALYTICAL
REAGENTS

By
Roy Henry Kinsey

December 12, 1949

Iowa State College
Ames Laboratory



Technical Information Service, Oak Ridge, Tennessee

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SYNTHESIS OF NEW ORGANIC
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Roy Henry Kinsey

ABSTRACT

The investigation of the preparation of three organic compounds, 2,2'-bipyrimidyl, 1,4-bis-(cyclohexoxy)-2,3-butanedionedioxime, and 2,2'-thenildioxime, analogs of useful analytical reagents in the specific or selective separation and/or determination of divalent metal ions has been carried out. The results of this study are listed below:

(1) 2,2'-Bipyrimidyl was not obtained by any of the methods investigated.

(2) Two new compounds, 2-chloropyrimidine and 2-bromopyrimidine were prepared and identified.

(3) The preparation of 1,4-bis-(cyclohexoxy)-2,3-butanedionedioxime was unsuccessful. However, some evidence for a molecular rearrangement of the intermediate carbonium ion was obtained from the analysis of the products of the reaction.

(4) 2,2'-Thenil was prepared by the acylation of thiophene by oxalyl chloride with anhydrous aluminum chloride as a catalyst. Yields of 5-12% were obtained by this method.

(5) The oximation of 2,2'-thenil produced a white crystalline compound which has the characteristics of a dioxime. An alcoholic solution of this compound in the presence of nickelous ions produced a bright orange colored precipitate. Palladous ions were similarly observed to form a yellow colored precipitate.

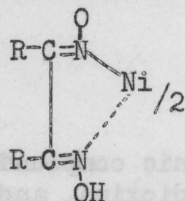
INTRODUCTION

In recent years certain organic reagents have found application in analytical chemistry because of their ability to form complex molecules with various metal ions. The general formulation of these complexes is identified with a characteristic structure, or active grouping, within the organic molecule. Two or more functional groups, in any one of a number of combinations, usually constitute this active grouping. Those molecules containing both an acid radical and a coordinating group form cyclic complexes of generally high stability with metallic cations. This process has been called chelation by Morgan and Drew(32) from which the cyclic complex derives the descriptive term chelate ring.

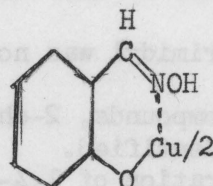
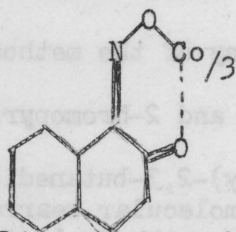
¹ M. S. Thesis submitted December 12, 1949. This work was performed under the direction of C. V. Banks.

Usually the metal is retained as a member of a five or six atom chelate ring. A few examples of the many combinations of functional groups are illustrated below:

a. 5-membered rings



b. 6-membered rings



The utility of these inner complex salts (i.e. non-ionic, metallic derivatives) in analytical chemistry is derived not only from their high stability but from a number of other desirable properties. Being non-polar and organic in character, they are usually colored, crystalline compounds of high molecular weight and definite composition.

The individual properties and application of the reagent are, however, somewhat dependent upon the remaining portion of the organic compound containing the active group. Thus the solubility, reactivity, and sensitivity of an organic reagent may be varied by derivatizing the parent compound (15) or by introducing the active group into another compound.

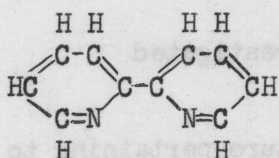
A series of twelve papers in the November, 1949, edition of Analytical Chemistry presents a comprehensive review of organic reagents and their role in modern chemistry. The search for new and more specific reagents and the development of derivatives of reagents already known is a growing industry within analytical research. Each new reagent or derivative provides more information regarding the essential requirements necessary to develop a more specific and useful reagent.

With this goal in mind, three organic compounds were suggested as possible reagents for divalent metal ions. The following discussion deals with the attempted methods of synthesis of 2, 2' -bipyrimidyl and 1, 4 -bis-(cyclohexoxy)-2, 3-butanedionedioxime, and the synthesis and properties of 2, 2' -thenildioxime.

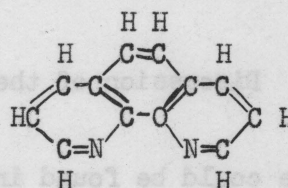
PROPOSED SYNTHESSES OF 2,2'-BIPYRIDYL

Introduction

In 1888 Blau (4) first recognized the formation of ferrous complexes while studying the metal complexes of 2,2'-bipyridyl. His interest led him to synthesize 1,10-phenanthroline nine years later (5). A comparison of the structures of these two compounds readily indicates Blau's reasoning and serves to illustrate the characteristic structure, or active functional group.

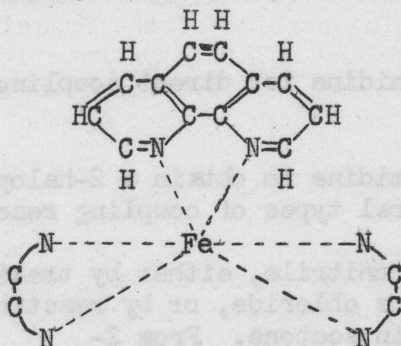


2,2'-Bipyridyl



1,10-Phenanthroline

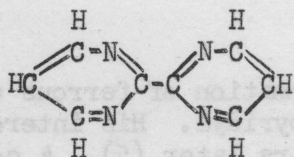
Analytical applications of these compounds did not appear until 1931, when Walden, Hammett and Chapman reported tris- (1,10-phenanthroline) iron-(II) sulfate, now called ferroin, as being a useful analytical tool (53). The structure of this ferrous complex is generally accepted as shown below:



The dotted lines represent secondary (Werner) valence forces.

Since 1931 the interest in this type of reagent has led to the preparation of numerous derivatives of 1,10-phenanthroline. An excellent summary of this work and the significant results has been prepared by Smith and Richter (46). The most recent advances in the preparation and application of polysubstituted 1,10-phenanthrolines and bipyridines have been presented in a paper by Brandt and Smith (7).

The cost of these chemicals is relatively high because of the poor yields that are obtained in their preparation. Therefore, following Blau's reasoning, a third molecule, 2,2'-bipyrimidyl, was postulated which contains a grouping similar to 1,10-phenanthroline and 2,2'-bipyridyl. The structural formula for this molecule is shown below:



2,2'-Bipyrimidyl

Discussion of the Methods Investigated

No evidence could be found in the literature pertaining to the successful preparation of this compound, or its derivatives. Howard, Lythgoe, and Todd (23) failed to obtain (2,2'-bipyrimidyl)-4,4',6,6'-tetramine through the condensation of malonamidine with ethyl oxalate. Yanai and Naito (56) were unsuccessful in coupling 2-chloro-4-benzyl-6-methylpyrimidine to obtain-4,4'dibenzyl-6,6'-dimethyl-2,2'-bipyrimidyl.

Of numerous possibilities, four methods of synthesis have been investigated.

I. The diazotization of 2-aminopyrimidine for direct coupling to produce the desired 2,2'-bipyrimidyl.

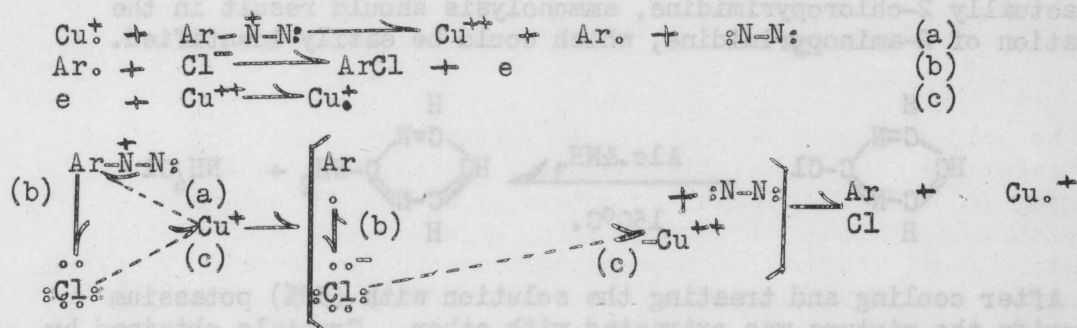
II. The diazotization of 2-aminopyrimidine to obtain a 2-halopyrimidine which in turn could be used in several types of coupling reactions.

III. The formation of 2-pyrimidinecarbonitrile, either by treatment of a 2-pyrimidinediazonium salt with cuprous chloride, or by reaction of a 2-halopyrimidine with potassium cyanide in acetone. From 2-pyrimidinecarbonitrile a two step synthesis was postulated to prepare 2-pyrimidinecarboxamide followed by a condensation of this compound with an aldehyde or ketone to form the second pyrimidine ring.

IV. The synthesis of oxalamidine and condensation of this with nitromalonaldehyde to produce 5,5'-dinitro-2,2'-bipyrimidyl.

Method I

The coupling of two aryl radicals by the Sandmeyer reaction has been accomplished by Ullmann and Forgan (52). They prepared 2,2'-dinitrobiphenyl by diazotization of 2-nitro-aniline and subsequent treatment with cuprous chloride. The mechanism of this reaction has been studied by Waters (54) who stated that the diaryl formation is a side reaction in the decomposition of aromatic diazo compounds. According to him (p.266), "The Sandmeyer and Gattermann reactions are considered to be catalysed decompositions of diazonium kations, involving a single electron transference and yielding neutral aryl radicals." He mentioned that the electron transference is facilitated by the easy release of an electron from a cuprous cation or from metallic copper. The following equations and mechanistic diagrams describe his theory.



In regard to the formation of diaryls, Waters believed that if a cuprous salt was gradually added to an aqueous solution of diazonium salt the frequency of occurrence of phase (c) would be small and any radicals produced by phase (a) would have the greatest chance of dispersing throughout the solution, to meet, and dimerize.

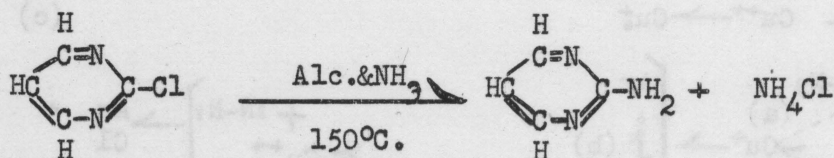
The successful application of the Sandmeyer reaction to the preparation of biaryls by other workers and the availability of 2-aminopyrimidine made it seem worth-while to try this method for the synthesis of 2,2'-bipyrimidyl.

No mention of 2-aminopyrimidine ever having been diazotized could be found in the literature. Tschitschibabin and Rjazancev (51) reported that 2-aminopyridine reacted considerably more slowly than aromatic amines with nitrous acid. They did, however, report a yield of 50 per cent of the 2-chloropyridine by treating 2-aminopyridine with nitrous acid in hydrochloric acid solution.

Applying a direct method for the formation of a diazonium salt, using sodium nitrite in 3 N hydrochloric acid solution, and subsequent addition of cuprous chloride yielded a small amount of a white, crystalline material, m.p. 63° C.

This compound was purified by sublimation, m.p. 67° C. and analyzed for carbon and hydrogen. From the results of this analysis an empirical formula was proposed, first on the basis of the formation of bipyrimidyl, i.e., $C_7H_5N_9$. Obviously no pyrimidine derivative could be assigned such a formula and a second sample was analyzed for nitrogen by the Dumas method. The total percentage of these three constituents only amounted to 69 per cent of the compound. A qualitative test indicated the presence of chlorine and a quantitative determination by the Parr bomb method indicated that the remaining 31 per cent of the compound was actually chlorine. From the total analysis a formula, $C_7H_5N_9Cl$, was computed. This fitted very nicely the formula for 2-chloropyrimidine.

To further establish the identity of this compound, a small sample was dissolved in an ammoniacal alcohol solution, sealed into a heavy glass tube and heated to 150° C. for two hours. If the compound was actually 2-chloropyrimidine, ammonolysis should result in the formation of 2-aminopyrimidine, which could be easily identified.



After cooling and treating the solution with (50%) potassium hydroxide the mixture was extracted with ether. Crystals obtained by evaporation of the ether had a m.p. 123-124° C. After sublimation of this product a mixed melting point was taken with pure 2-aminopyrimidine. The observed value was 126-127° C., while the literature value was given as 127-128° C.

When the 2-chloropyrimidine was recrystallized from hot water, long, needle-like crystals were obtained, m.p. 63° C. The nitrogen analysis of this compound was consistently low. However, the percentage of nitrogen, calculated on the basis of a monohydrate, agreed very well with the observed values.

Many variations in the diazoatization procedure were employed in an attempt to increase the yield of 2-chloropyrimidine or effect a direct coupling to 2,2'-bipyrimidyl. Such variables as acid concentration, rate of addition of sodium nitrite solution, and temperature were thoroughly investigated to obtain the most effective conditions.

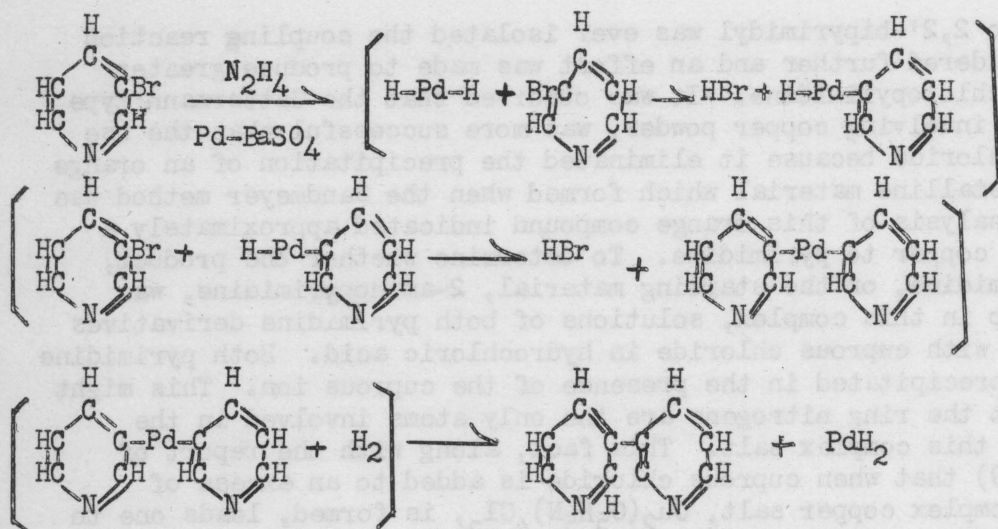
Schoutissen(43) mentioned the use of phosphoric acid and nitrosylsulfuric acid for weakly basic amines. Hodgson and Walker (22) suggested hot glacial acetic acid as a substitute for the phosphoric acid, in some cases. Neither of these methods were effective in diazotizing 2-aminopyrimidine.

Since no 2,2'-bipyrimidyl was ever isolated the coupling reaction was not considered further and an effort was made to produce greater yields of 2-chloropyrimidine. It was observed that the Gattermann type of reaction, involving copper powder, was more successful than the use of cuprous chloride because it eliminated the precipitation of an orange colored, crystalline material which formed when the Sandmeyer method was employed. Analysis of this orange compound indicated approximately a 1:1 ratio of copper to pyrimidine. To determine whether the product, 2-chloropyrimidine, or the starting material, 2-aminopyrimidine, was being tied up in this complex, solutions of both pyrimidine derivatives were treated with cuprous chloride in hydrochloric acid. Both pyrimidine derivatives precipitated in the presence of the cuprous ion. This might indicate that the ring nitrogens are the only atoms involved in the formation of this complex salt. This fact, along with the report of Marukhyan (29) that when cuprous chloride is added to an excess of pyridine a complex copper salt, $\text{Cu}_2(\text{C}_5\text{H}_5\text{N})_4\text{Cl}_2$, is formed, leads one to propose a similar formula, $\text{Cu}_2(\text{C}_4\text{H}_5\text{N}_3)_2\text{Cl}_2$, for the complex copper salt in the case of 2-aminopyrimidine. A study of the effect of pH on the formation of the precipitate showed that the complex dissolved in solution below a pH of 0.5, and no precipitate would form above a pH of 4.0.

Yields of 2% to 24% of 2-chloropyrimidine were obtained by using the direct method of diazotization in an aqueous medium, followed by the Gattermann procedure for replacing the amine with a halide. In general, better yields were obtained when the rate of addition of 10 N sodium nitrite solution was very slow.

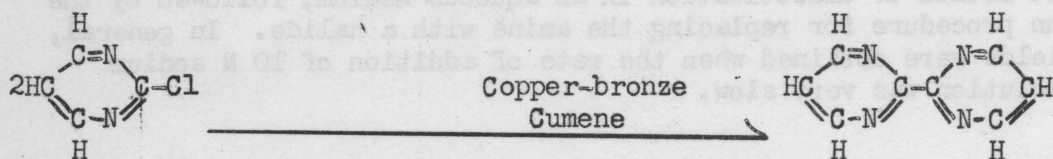
Method II

With this new source of 2-halopyrimidine available, the second proposed method of synthesis was studied. Three different paths were considered. The first choice was suggested from the work of Busch and co-workers (9) who had successfully effected the formation of 3,3'-bipyridyl by a method of catalytic hydrogenation of 3-bromopyridine, under the influence of palladium.



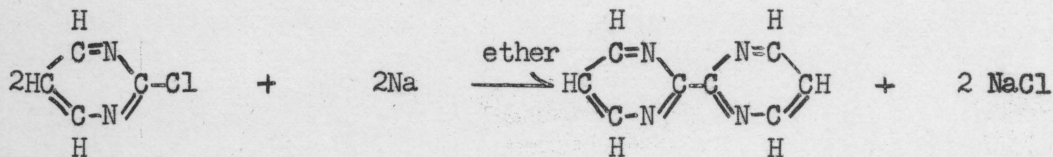
The above mechanism was proposed by Busch (9) as one possible explanation of the partial reduction of aryl halide.

A second, less desirable method would involve an Ullmann reaction as follows:



Yanai and Naito (56) obtained 2,2'-di-n-butyl-6,6'-dimethyl-4,4'-bipyrimidyl by heating 2-n-butyl-6-methyl-4-chloropyrimidine in cumene with a copper-bronze catalyst. They also mentioned that the coupling of pyrimidines in the 2-position was more difficult.

The third possibility was coupling by a Wurtz-Fittig type reaction as follows:



Klason (27) reacted bromobenzene and sodium with cyanuric chloride to obtain a mixture of triphenyltriazine and chlorodiphenyltriazine.

From a survey of the literature regarding these methods it was felt that the 2-bromopyrimidine would be more suitable for such a reaction.

Therefore, applying the same general procedure as was used in preparing 2-chloropyrimidine, using 48% hydrobromic acid and sodium nitrite, it was found that yields of only 4% of a white crystalline product, m.p. 53-54° C., could be obtained.

Since the bromine determination by a Parr method was relatively accurate and in excellent agreement with the calculated percentage of bromine, on the basis of 2-bromopyrimidine, this method served as the means of identifying the compound as the 2-bromo derivative.

The low yield of 4% was in agreement with Tschitschibabin and Rjazancev (51) who reported very small yields of 2-bromopyridine, due to the action of nitrous acid on concentrated hydrobromic acid to give bromine.

Here again additional methods were investigated. Richter (39) described a method of replacing amino groups with bromine by treating the amine in acetic acid with a sodium nitrite solution. A mixture of hydrobromic acid and bromine was then added to this solution. Applying this method to 2-aminopyrimidine resulted in the formation of a clear, water insoluble oil which had a boiling point of 147° C. This compound was not identified or the procedure repeated since it obviously was not the desired 2-bromopyrimidine. The 2-iodopyrimidine was never obtained by any of the methods investigated.

Although Busch (9) preferred the use of bromo derivatives in his work he did obtain 20% of biphenyl from 2-chlorobenzene. Applying his method to 2-chloropyrimidine, only micro quantities of white crystals were obtained. The compound, unidentified due to the small yield, did have the faculty of producing a deep red color with ferrous ion. Since this is the characteristic color of the ferroin complex, it was felt that this might be 2,2'-bipyrimidyl although repeated attempts did not provide sufficient compound for analysis.

While Busch employed both hydrazine and methyl alcohol as sources for the hydrogen in the catalytic reduction reaction, Mayo and Hurwitz (30) recently reported the effect of experimental conditions on the yield of biphenyl from bromobenzene. They modified the procedure, as given by Busch, in that they only used methanol as the reducing agent.

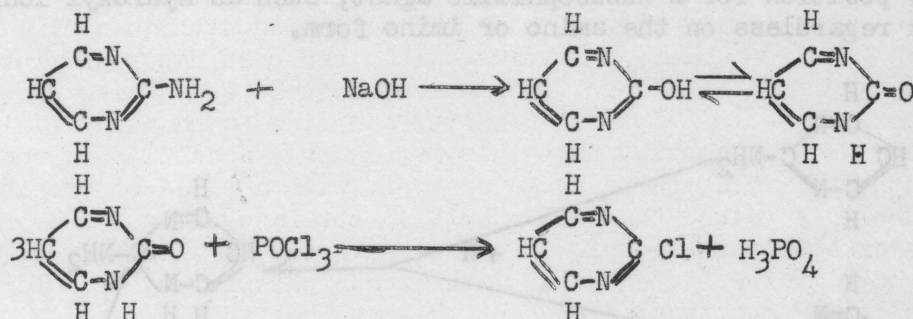


By this method they obtained biphenyl in yields up to 50%. Busch reported as high as 76% biphenyl in his work.

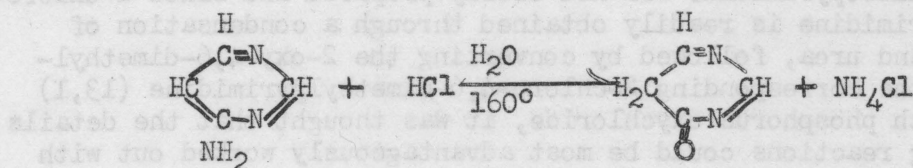
Both 2-chloropyrimidine and 2-bromopyrimidine were treated according to this modified method. No product was isolated although halide cleavage was observed in both reactions.

Coupling of 2-chloro-5-nitropyrimidine by the catalytic hydrogenation method was not attempted because of the possibility of reducing the nitro group.

Since the 2-amino-5-nitropyrimidine was so readily converted to the hydroxy compound by the action of alkali, it was thought that 2-aminopyrimidine might be treated in a similar manner to give a rapid and economical method for obtaining the 2-chloropyrimidine.



Buchman and Williams (8) reported a quantitative conversion of 6-aminopyrimidine to the corresponding oxyprymidine by action of concentrated hydrochloric acid at 160°.

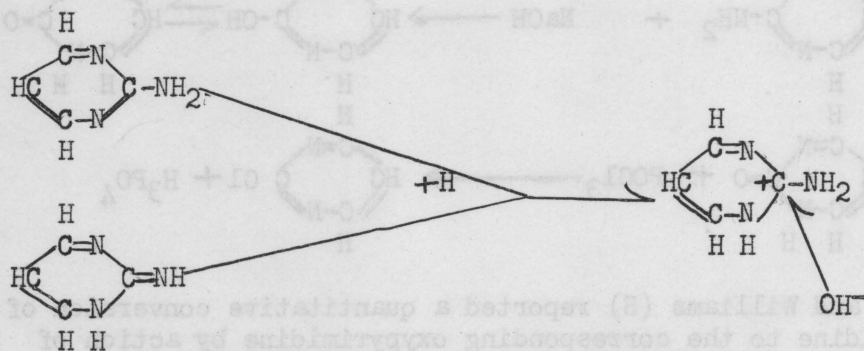


2-Aminopyrimidine was refluxed in both acid and alkaline solutions and although the hydrolysis of the amine was detected in each case, by collection of the amount of ammonia released, no 2-oxyprymidine was ever isolated. A yield of less than 1% of 2-chloropyrimidine was obtained by evaporation of the acid hydrolysis solution of 2-aminopyrimidine to near dryness and refluxing the yellow residue in excess phosphorus oxychloride.

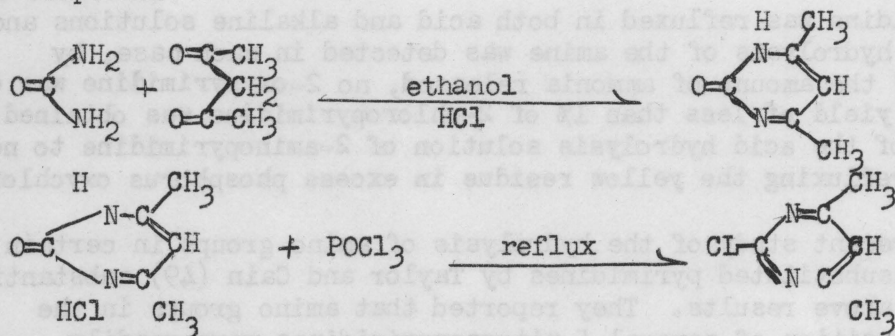
A more recent study of the hydrolysis of amino groups in certain 2,4,5,6-tetrasubstituted pyrimidines by Taylor and Cain (49) substantiates, in part, the above results. They reported that amino groups in the 4- and/or 6-position of several 5-nitrosopyrimidines were readily replaced by hydroxyl groups upon boiling the compound for a short time with 6N hydrochloric acid. An amino group in the 2-position was not removed under these mild conditions, however. Taylor and Cain found that prolonged heating of substituted 2-aminopyrimidines in acid solution resulted instead in ring cleavage, as shown by the isolation of guanidine from the reaction mixture. These authors conclude that the resistance toward acid hydrolysis of an amino group in the 2-position

of a pyrimidine ring might indicate that it exists predominantly in the amino rather than the imino form. This conclusion was based on the fact that the double link $C=N$, as in imines, is much less stable toward hydrolysis than the single link $C-N$ (45).

Taylor and Cain apparently neglected to consider the effect that a hydrogen ion would have on 2-aminopyrimidine. The resonance structures below illustrate this effect and indicate that the 2-position would be a likely position for a nucleophilic agent, such as hydroxyl ion, to attack regardless on the amino or imino form.



Since 2-chloropyrimidine was not easily prepared and since 2-chloro-4,6-dimethylpyrimidine is readily obtained through a condensation of acetylacetone and urea, followed by converting the 2-oxy-4,6-dimethylpyrimidine to the corresponding 2-chloro-4,6-dimethylpyrimidine (13,1) by reaction with phosphorus oxychloride, it was thought that the details of the coupling reactions could be most advantageously worked out with this compound.



However, the presence of the two methyl groups in the 4 and 6 position apparently produced a deactivation effect, at least in all cases where this compound was employed as starting material it was recovered as the only product. Even in the presence of potassium

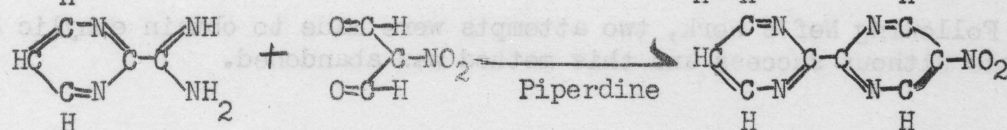
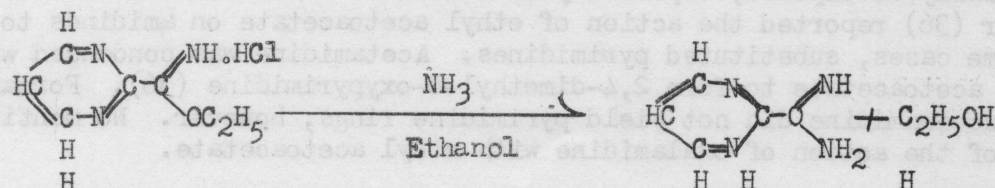
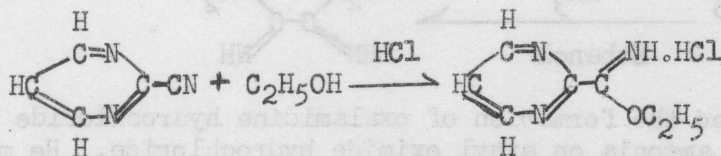
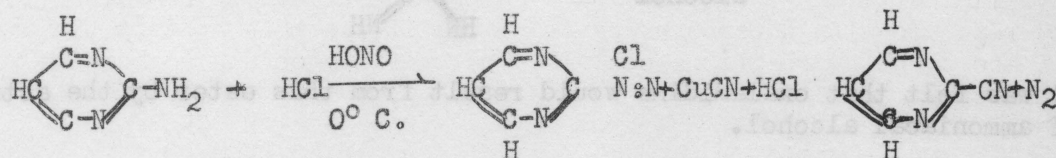
permanganate, which was added to an aqueous solution of the 2-chloro-4,6-dimethylpyrimidine and refluxed for ten hours, the original 2-chloro-4,6-dimethylpyrimidine was recovered and no dicarboxylic acid or 2-chloropyrimidine was isolated.

It might be expected that bromine would be more easily replaced than chlorine. Therefore, the preparation of 2-bromo-4,6-dimethylpyrimidine was considered.

Golding and Senear (20) obtained yields up to 61% of 2,4,6-tri-bromopyrimidine by treating barbituric acid with phosphorus oxybromide. When 2-oxy-4,6-dimethylpyrimidine was treated with phosphorus oxybromide only traces of a very lachrymatory compound resulted. In all cases it appeared that the 4,6-dimethyl-2-oxypyrimidine was decomposed, leaving a tarry residue.

Method III

The third general method proposed for the preparation of 2,2'-bipyrimidyl, as mentioned above, was by way of 2-pyrimidinecarbonitrile. Cuprous cyanide was used in hopes of obtaining 2-pyrimidinecarbonitrile from pyrimidinediazonium chloride, which could then be converted to 2-pyrimidinecarboxamide. This compound might be condensed with a suitable ketone or aldehyde to form the second pyrimidine ring. The following reactions illustrate this proposed synthesis:

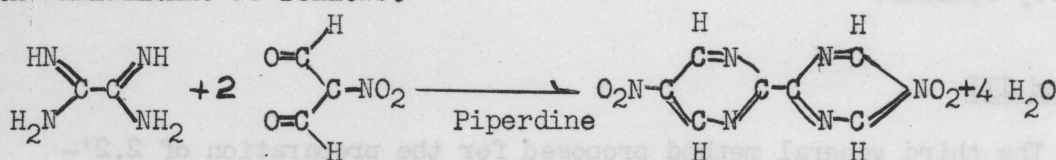


However, when 2-pyrimidinediazonium chloride was treated with cuprous cyanide by the Sandmeyer reaction, only 2-chloropyrimidine was isolated and as explained above, some of the pyrimidine was precipitated as the copper-(I)-pyrimidine complex.

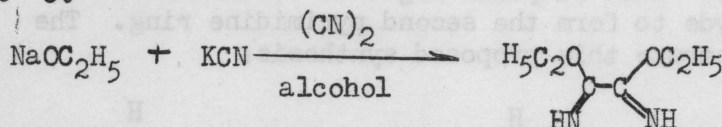
Reaction of 2-chloropyrimidine with an alcoholic solution of potassium cyanide also failed to yield any 2-pyrimidinecarbonitrile. Similar treatment of 2-chloro-5-nitropyrimidine was not investigated.

Method IV

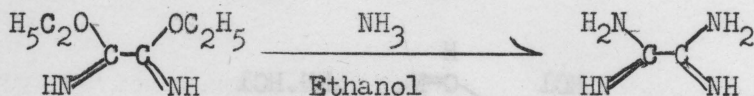
The fourth general plan was to shift the method of attack completely away from pyrimidine derivatives, building the dipyrimidyl molecule through a series of reactions. One such synthesis was proposed, starting with oxalamidine as follows:



Nef (34) reported the formation of ethylic diimido oxalate, when cyanogen was passed into a solution of sodium ethoxide in excess alcohol at 0° C.



It was felt that oxalamidine would result from this ester by the action of ammoniacal alcohol.

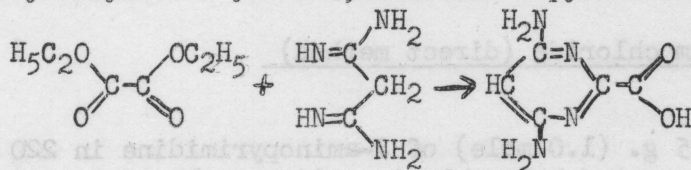


Pinner (35) reported the formation of oxalamidine hydrochloride by the action of alcoholic ammonia on ethyl oximide hydrochloride. He mentioned further, that although this compound could be recrystallized from water it was easily decomposed, especially in solution. In another series of papers, Pinner (36) reported the action of ethyl acetoacetate on amidines to form, in some cases, substituted pyrimidines. Acetamidine was condensed with ethyl acetoacetate to form 2,4-dimethyl-6-oxypyrimidine (36). Formamidine and succinamidine did not yield pyrimidine rings, however. No mention was made of the action of oxalamidine with ethyl acetoacetate.

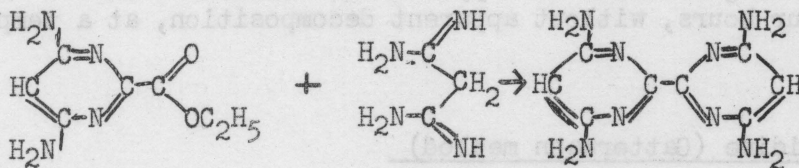
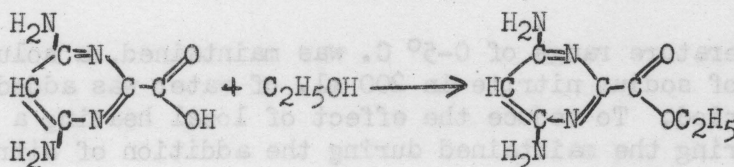
Following Nef's work, two attempts were made to obtain ethylic diimido oxalate without success and this method was abandoned.

Discussion of Proposed Methods for Future Research

Howar, Lythgoe, and Todd (23) have reported numerous condensation reactions involving malonamidine and various esters. Among these esters was ethyl oxalate which the authors used in hopes of obtaining (2,2'-bipyrimidyl)-4,4',6,6'-tetramine. Actually, however, they found that only one ester group reacted with malonamidine while the second ester group was hydrolysed to yield 4,6-diamino-2-pyrimidinecarboxylic acid (23).

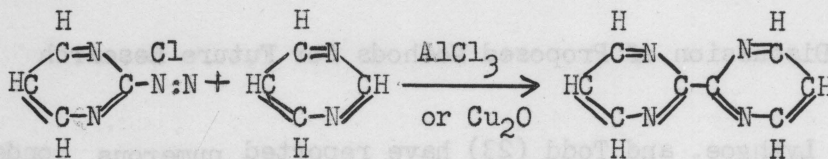


They did not mention the possibility of reesterifying this acid and repeating the condensation with another mole of malonamidine. If such were possible (2,2'-bipyrimidyl)-4,4',6,6'-tetramine should result.



The removal of the amino groups might be accomplished by hydrolysis to the corresponding hydroxy derivative by refluxing the (2,2'-bipyrimidyl)-4,4',6,6'-tetramine in 6N hydrochloric acid (49). The replacement of 4,6-hydroxypyrimidine to the corresponding 4,6-dichloropyrimidine and subsequent replacement of the halo groups with hydrogen by the action of zinc dust has been reported by Gabriel (19).

Another possibility involves 2-pyrimidinediazonium chloride. The dry diazonium salt of aniline has been reacted with benzene in the presence of anhydrous aluminum chloride to give biphenyl (50). The reaction may also be carried out in alkaline solution, which may be more convenient and safer, if cuprous oxide is used as catalyst.



Experimental Work

2-Pyrimidinediazonium chloride (direct method)

A solution of 95 g. (1.0 mole) of 2-aminopyrimidine in 220 ml. (3.0 moles) of concentrated hydrochloric acid was placed in a 1-liter, three-necked flask. The latter was equipped with a mechanical stirrer, a thermometer, and a dropping-funnel the stem of which extended below the liquid surface. The solution was chilled by an ice-salt bath and stirred rapidly to precipitate the 2-aminopyrimidine hydrochloride as fine crystals.

While a temperature range of 0-5° C. was maintained, a solution of 70 g. (1.0 mole) of sodium nitrite in 200 ml. of water was added dropwise over a 10 hour period. To reduce the effect of local heating a very slow rate of stirring the maintained during the addition of nitrite.

The resulting solution of 2-pyrimidinediazonium chloride was stored for twenty-four hours, without apparent decomposition, at a temperature below -15° C.

2-Chloropyrimidine (Gattermann method)

Sixty-three g. (1.0 mole) of commercial copper powder was added portionwise, with mild stirring, to the cold solution of 2-pyrimidinediazonium chloride prepared above. On completion of this addition the mixture was heated slowly with stirring to 50°C. When the evolution of nitrogen had ceased the mixture was cooled before transferring it into a 3-liter, modified Claisen flask for steam distillation. A 20% solution of sodium hydroxide was added cautiously to the acid solution until the pH was between 8 and 9. This dissolved a large portion of the flocculent material which precipitated upon addition of the copper. The alkaline mixture was heated to 90° C. before steam was passed into the solution. An air condenser was used since the product crystallized before reaching the receiving flask when a water-cooled condenser was employed. The receiving flask was cooled by an ice bath to prevent loss of the volatile product, and to minimize the amount of

2-chloropyrimidine that might dissolve in the distillate.

After one liter of the distillate had been collected, the crystalline product (8.5 g.) was filtered off. The filtrate was extracted five times with 100 ml. portions of ether. After drying the ether solution over calcium chloride the solvent was removed by vacuum distillation leaving 19.0 g. of residue.

Recrystallization of this material from water yielded a compound which melted at 63°C . This material was found to contain 21.57% nitrogen indicating that it might be 2-chloropyrimidine monohydrate which would contain 21.15% nitrogen.

This product was then recrystallized from petroleum ether (Skellysolve B, b.p. range $60-80^{\circ}\text{C}$.) yielding a material with a m.p. of 67°C that analyzed as follows:

	Found*	Calculated**
Carbon	42.0%	41.92%
Hydrogen	2.5	2.62
Nitrogen	25.0	24.46
Chlorine	30.9	31.00

*These values are the average of two analyses of each component.

**On the basis of 2-chloropyrimidine.

The total of 27.5 g. represented a 24% yield of 2-chloropyrimidine.

Proof of structure of 2-chloropyrimidine by ammonolysis.

A solution of 1.8 g. (0.015 mole) of 2-chloropyrimidine in 15 ml. of concentrated ammonium hydroxide and 10 ml. of ethanol was sealed in a heavy glass tube. This mixture was heated to 150°C . for two hours.

On cooling, the contents of the tube were washed out with absolute alcohol. The alcohol solution was heated to boiling and filtered hot. The filtrate was treated with a 33% solution of potassium hydroxide and then extracted with two 20 ml. portions of ether. After drying the ether over calcium chloride, the solvent was removed by evaporation leaving a residue, m.p. $123-124^{\circ}\text{C}$. This crude product was sublimed and mixed with an equal portion of pure 2-aminopyrimidine. The mixed melting point was $126-127^{\circ}\text{C}$. The literature lists the melting point of 2-aminopyrimidine as $127-128^{\circ}\text{C}$. thus indicating that 2-chloropyrimidine had been converted to 2-aminopyrimidine.

2-Chloropyrimidine (Sandmeyer method)

A solution of 55 g. (0.5 mole) of cuprous chloride in 100 ml. of concentrated hydrochloric acid was heated to boiling in a 1-liter beaker. A cold solution of 2-pyrimidinedizaonium chloride, prepared as above from 95 g. (1.0 mole) of 2-aminopyrimidine, was slowly added dropwise to the warm (50° C.) cuprous chloride solution. A large quantity of yellow colored solid precipitated. On completion of the addition, a 20% solution of sodium hydroxide was carefully added, with cooling, until a pH of 8 had been attained. The solid matter was still present as a brown colored, curdy mass.

This alkaline solution, including the brown colored mass, was steam distilled. No product was obtained from the distillate. Extraction of the residual mixture resulted in recovery of only a small portion of the original starting material. The remainder was tied up in the brown colored sludge which originally precipitated as a yellow colored, silken mass. Further investigation of this precipitate proved that a copper-pyrimidine complex was being formed which seriously retarded the replacement reaction.

Analysis of the copper-pyrimidine complex

Qualitative: A solution of cuprous chloride was added to aqueous solutions of 2-aminopyrimidine and 2-chloropyrimidine. In both cases, a precipitate developed. It was observed that when the addition was made in a pH range of 1 to 2.5, the precipitate was orange in color and crystalline. From a pH of 2.5 to 4.5 the precipitate was yellow in color and amorphous.

Ammonium hydroxide partially dissolved the orange crystalline material, forming a deep blue solution of tetramine copper (II) chloride, $\text{Cu}(\text{NH}_3)_4 \text{Cl}_2$.

Quantitative: Solution of cuprous chloride was added to a saturated solution of 2-aminopyrimidine and the resulting orange colored precipitate was oven dried, at 110° C., to constant weight. This dry precipitate was dissolved in a solution of 100 ml. of water containing 10 drops of concentrated nitric acid. After destroying the organic matter the clear acid solution was cooled and excess 1 N silver nitrate solution was added to precipitate any chloride ion. The precipitate was allowed to digest for eight hours in the dark before being removed by filtration.

The filtrate was treated with an excess of concentrated hydrochloric

acid to remove any excess silver. After a period of digestion the silver chloride was filtered off.

This filtrate was taken to near dryness with sulfuric acid and then diluted to 200 ml. before the copper was removed by electrodeposition. The results of the analysis are shown below:

Complex taken, g.	% Copper found	% Chlorine found	Mole ratio Cu: 2-amino- pyrimidine	Mole ratio Cl: 2-amino- pyrimidine
0.1892	30.8	19.9	0.90	1.05
0.1245	30.0	20.3	0.87	1.06
Average	30.4	20.1	0.88	1.05

These data indicate that the complex might be 2-aminopyrimidine-copper (I) chloride, $\text{Cu}(\text{C}_4\text{H}_5\text{N}_3)\text{Cl}$, which would contain 32.5% copper and 18.0% chlorine.

2-Pyrimidinediazonium sulfate (Phosphoric acid method)

A solution of 10 g. (0.1 mole) of 2-aminopyrimidine in 60 ml. of concentrated sulfuric acid was cooled to 0°C . in a 500 ml. three-necked flask. The latter was equipped with a mechanical stirrer, dropping-funnel, and thermometer. A solution of 9 g. (0.1 mole) of sodium nitrite in 60 ml. of concentrated sulfuric acid was added to the cold sulfuric acid solution of the 2-aminopyrimidine. A temperature of 0°C . was maintained by surrounding the reaction flask with an ice-salt mixture. The reaction mixture was stirred vigorously and to it was added dropwise 240 ml. of concentrated phosphoric acid over a four hour period. After thirty minutes of standing at 0°C ., 8 g. of urea was added to decompose any excess nitrous acid.

This reaction mixture was divided into three portions and the following methods were employed:

Attempted preparation of 2-iodopyrimidine

A saturated solution of potassium iodide was added dropwise to the 2-pyrimidinediazonium sulfate solution at 0°C . The violet colored reaction mixture was neutralized with excess of a 20% solution of sodium hydroxide producing a pale yellow colored, alkaline solution. This solution was steam distilled. No 2-iodopyrimidine was isolated.

Attempted preparation of 2-bromopyrimidine

A solution of 15 g. (0.09 mole) of bromine and 15 g. (0.12 mole) of potassium bromide in 100 ml. of water was added dropwise to the second portion of the 2-pyrimidinediazonium sulfate solution containing 200 g. of crushed ice. To this mixture, after one hour of standing, 6 g. of copper powder was added. Upon treating this mixture as described in the Gattermann procedure above, no 2-bromopyrimidine was isolated.

Attempted preparation of 2-chloropyrimidine

To a hot solution of 150 ml. of concentrated hydrochloric acid and 45 ml. of water were added 10.8 g. (0.04 mole) of copper sulfate, 5.4 g. (0.1 mole) of sodium chloride, and 30 g. (0.5 mole) of copper powder. This mixture was refluxed until a clear solution resulted and then it was cooled to 0° C. On addition of the cuprous chloride solution to the cold solution of 2-pyrimidinediazonium sulfate and copper-pyrimidine complex was formed as a curdy, yellow colored precipitate. In hopes of destroying this complex the mixture was neutralized with concentrated ammonium hydroxide. The resulting deep blue solution was extracted three times with 50 ml. portions of ether. 2-Chloropyrimidine was not isolated from the combined ether extracts.

Unsuccessful test for 2-pyrimidinediazonium sulfate

In view of the unsuccessful results another solution of 2-pyrimidine-diazonium sulfate was prepared in a manner identical to that described above. This solution was coupled with a solution of 2.4 g. (0.16 mole) of β -naphthol in 15 ml. of glacial acetic acid. A deep violet color was obtained which changed to brown with stirring. The expected azo compound was poured onto ice and the solid brown precipitate removed by filtration.

The dried solid weighed 2.32 g. and after recrystallization had a m.p. of 122° C., which is identical with the literature value for the melting point of β -naphthol. The weight and melting point of this material would seem to indicate that no coupling had occurred, and from the negative results above it seemed that the phosphoric acid method was not favorable to the preparation of the diazonium salt.

2-Chloro-4,6-dimethylpyrimidine

This compound was prepared according to the methods of Evans (13) and Angerstein (1). A condensation of acetylacetone with urea in the presence of hydrochloric acid was followed by the replacement of the keto group by chlorine, using phosphorus oxychloride.

Attempted preparation of 4,6-dimethyl-2-pyrimidinecarbonitrile

Method A. A suspension of 22 g. (0.15 mole) of 2-chloro-4,6-dimethylpyrimidine and 13.5 g. (0.15 mole) of cuprous cyanide in 30 ml. of dry pyridine was placed in a three-necked flask. The latter was equipped with a mechanical stirrer, reflux condenser, and thermometer. The mixture was stirred rapidly and maintained at reflux temperature by means of an electric mantle.

After five hours, the mixture had changed from a suspension of reactants to a dark brown colored tar. On cooling, the tarry material solidified to a hard, brittle mass from which no 4,6-dimethyl-2-pyrimidinecarbonitrile or starting material was recovered.

Method B. A solution of 10 g. (0.07 mole) of 2-chloro-4,6-dimethylpyrimidine and 4 g. (0.8 mole) of sodium cyanide in 10 ml. of water and 18 ml. of ethyl alcohol was placed in a 100 ml. flask equipped with a reflux condenser. This solution was refluxed for two hours, at which time the condenser was replaced by a Claisen adapter and the condenser was rearranged for vacuum distillation. Sixty per cent of the starting material was recovered from the distillation. 4,6-Dimethyl-2-pyrimidinecarbonitrile was not obtained from the distillate or residue.

Attempted preparation of 2-pyrimidinecarbonitrile

A solution of 2-aminopyrimidinediazonium chloride was prepared from 9.5 g. (0.1 mole) of 2-aminopyrimidine as described above. This cold solution was transferred to a 1-liter beaker and placed in a hood. A solution of 25 g. (0.1 mole) of copper sulfate in 150 ml. of hot water was added to the 2-aminopyrimidinediazonium chloride solution. To this mixture, 28 g. (0.57 mole) of crystalline potassium cyanide was added in small portions. A vigorous reaction was observed after each addition and the solution turned to a dark purple color.

After addition was complete the solution was treated with enough 20% sodium hydroxide solution to attain a pH of 8. This alkaline mixture was transferred to a modified Claisen flask for steam distillation. The crystals that were obtained from the distillate were identified as 2-chloropyrimidine. The yield was very low and no evidence for the formation of 2-pyrimidinecarbonitrile was found.

When the cold solution of 2-pyridinediazonium chloride was added to a solution of 122 g. (0.5 mole) of copper sulfate and 140 g. (2.1 moles) of potassium cyanide in 600 ml. of water at 45° C. the 2-chloropyrimidine was obtained in yields up to 20%.

Attempted preparation of 4,4',6,6'-tetramethyl-2,2'-bipyrimidyl

To 4 g. (0.17 mole) of finely divided sodium in 100 ml. flask, equipped with a reflux condenser, was added 14.2 g. (0.1 mole) of 2-chloro-4,6-dimethylpyrimidine dissolved in a minimum of ether. No evidence of a reaction was observed until 5 ml. of ethyl acetate was added to the mixture as a catalyst. This solution was refluxed for thirty-six hours.

Just enough alcohol was added to remove any excess sodium and then water was added to dissolve the salt that had formed. At this point the ether layer was pink in color, and the aqueous layer was colored orange. After drying the ether layer over sodium sulfate it was distilled. Three fractions were collected; ether, alcohol, and a yellow oil. Attempts to purify and identify the oil failed.

Attempted preparation of 2-iodo-4,6-dimethylpyrimidine

A solution of 14 g. (0.1 mole) of 2-chloro-4,6-dimethylpyrimidine in a minimum of acetone was added to a solution of 15 g. (0.1 mole) of sodium iodide in 100 ml. of acetone. The mixture was refluxed for seventy-two hours without any visible change in the reactants. The starting materials were recovered.

Attempted preparation of 2,2'-bipyrimidyl

A solution of 5 g. of sodium hydroxide in 15 ml. of water and 100 ml. of methanol was placed in a heavy glass tube containing 11 g. (0.1 mole) of 2-chloropyrimidine and 10 g. of 1% Pd-BaSO₄. The Pd-BaSO₄ catalyst was prepared according to the method described by Mozingo (33). Three ml. of hydrazine hydrate was added to this mixture just before sealing off the tube. The sealed tube was placed in a metal jacket and heated to 90° C. for one hour.

After cooling, the tube was opened and the catalyst was filtered off. The palladium residue was washed by decantation with 50 ml. of hot methanol. The combined filtrates were acidified with concentrated hydrochloric acid before removal of the alcohol by steam distillation. The residue from this distillation was treated with just enough 20% sodium hydroxide solution to make it basic and then redistilled.

No product was isolated in this distillate. On cooling, however, the residue of the distillation contained a few crystals, m.p. 110-111°C. This material was not identified because of the small yield. However, an aqueous solution of the crystals when treated with ferrous sulfate had the faculty of producing a deep red colored solution.

Hydrolysis of 2-aminopyrimidine (acid catalysed)

A solution of 10 g. (0.1 mole) of 2-aminopyrimidine in 100 ml. of concentrated hydrochloric acid was placed in a 500 ml. flask fitted with a reflux condenser. After four hours of reflux the flask was removed and cooled. The solution was transferred to a Claisen flask fitted with a dropping-funnel and connected to a steam line. A solution of 20% sodium hydroxide was added from the dropping-funnel and steam was passed into the alkaline solution. The condenser tip was extended below the surface of the beaker of distilled water to collect any ammonia that might be evolved. The distillate was titrated against 0.5N hydrochloric acid from which it was calculated that 40% of the starting material had been hydrolysed.

The yellow colored solution remaining in the Claisen flask was extracted with three 25 ml. portions of ether. A small amount of 2-aminopyrimidine was recovered from this ether solution by evaporation of the solvent.

The aqueous layer was adjusted to a pH of 7 and extracted with three 50 ml. portions of n-butyl alcohol. A variety of crystals were left in the flask when the alcohol was removed by vacuum distillation. The bottom of the flask contained an inorganic substance which was not identified. The center portion of the flask was coated with a crystalline material, m.p. 161°C ., and the upper portion of the flask was coated with sublimed 2-aminopyrimidine.

The yield of this crystalline product, m.p. 161°C . was so small that identification was not attempted. The hydrolysis of 2-aminopyrimidine was repeated in a manner similar to that described above but instead of determining the amount of ammonium chloride that was formed, the acidic solution was taken to dryness. The yellow colored salt that resulted was treated with excess phosphorus oxychloride at reflux temperature. After removal of any excess phosphorus oxychloride by vacuum distillation, the residue was poured onto ice. This mixture was extracted twice with 20 ml. portions of ether. Less than 1% of 2-chloropyrimidine was isolated on evaporation of the ether.

Attempted hydrolysis of 2-aminopyrimidine (base catalysed)

To a solution of 30% sodium hydroxide in a modified Claisen flask was added a solution of 5 g. (0.05 mole) of 2-aminopyrimidine in 20 ml. of ethanol. This alkaline solution was refluxed gently while any escaping vapor was collected in an acidic solution of known concentration. After two hours of refluxing this mixture the acid solution in the condenser trap was titrated against 0.1N sodium hydroxide to determine how much ammonia had been released by the hydrolysis of the amine. It was found

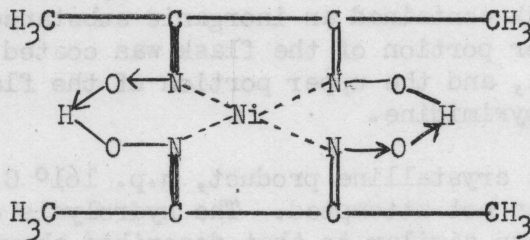
that only 6.6% of the amine had been hydrolysed. Ether extraction of the alkaline residue recovered most of the starting material.

PROPOSED SYNTHESIS OF 1,4-BIS-(CYCLOHEXOXY)-2,3-DIONEDIOXIME

Introduction

A number of 1,2-dioximes have been reported as suitable reagents in the determination of nickel and palladium. Diehl (12) presented an interesting review of the history and proof of the chelate structure involved, as well as a survey of the important dioximes and their analytical applications.

Using the dimethylglyoxime as an example, the structural group responsible for the formation of an inner complex with divalent nickel is illustrated below:

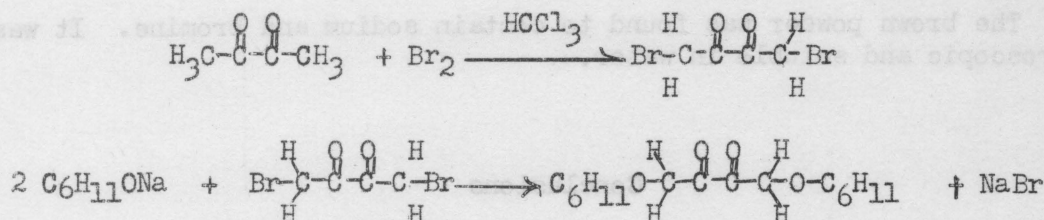


The dotted lines represent the secondary (Werner) valence forces. The arrows indicate hydrogen bonding, as assumed by Brady (6) on the basis that hydroxyl groups in this compound are found to be inactive.

Replacement of these methyl groups with other aliphatic, aromatic, or heterocyclic groups exemplifies the introductory remark concerning the effect of solubility and sensitivity by replacement of substituent groups. Dimethylglyoxime is considered sparingly soluble in water, while 1,2-cyclohexane-dionedioxime and α -naphthylidioxime are reported as water soluble. α -Benzildioxime and benzoylmethylglyoxime are insoluble in water. This limited water solubility in many of the dioxime reagents requires the use of alcohol or acetone in the analytical procedure, which is not desirable. For this reason the preparation of 1,4-bis(cyclohexoxy)-2,3-dionedioxime was proposed to determine its solubility in water and suitability as an analytical reagent.

Discussion of the Method Investigated

By application of the Williamson reaction it was hoped that a series of bis-derivatives of butane-2,3-dione might be prepared from 1,4-dibromo-2,3-butanedione and sodium alkoxides. Sodium cyclohexoxide was used to study this proposed reaction and 1,4-dibromo-2,3-butanedione was prepared by bromination of diacetyl (42).



Actually none of the desired diketone was ever isolated and this led to careful analysis of the reaction mixture for products that might explain the mechanism involved.

The first set of reactions between 1,4-dibromo-2,3-butanedione and sodium cyclohexoxide were carried out in an excess of cyclohexanol. Vacuum distillation of this mixture removed the alcohol and left a brown amorphous solid with characteristics similar to a sodium salt. This same saltlike product was obtained when sodium ethoxide was used in place of sodium cyclohexoxide.

To more clearly examine the possibility that cyclohexanol was being formed in the reaction, a second series of reactions was carried out with exact amounts of sodium cyclohexoxide and 1,4-dibromo-2,3-butanedione suspended in a medium of anhydrous dioxane. After a period of reflux a brown powder was filtered off and dioxane was removed from the filtrate by vacuum distillation. Two fractions were separated, leaving a resinous mass in the distillation flask. The first fraction was dioxane, the second fraction represented nearly a quantitative return of cyclohexanol from the amount of sodium cyclohexoxide employed.

A series of qualitative tests was carried out on the alcohol fraction in an attempt to determine the character of the impurity which was established to be present in micro amounts by a comparison of refractive indices.. A positive test was obtained for the presence of an ester, by application of the hydroxamate test (11). A small amount of halide was also found present when silver halide precipitated on the addition of silver nitrate to an acid solution of the alcohol. Although the alcohol was treated with phenylhydrazine and 3,5-dinitro-phenyl hydrazine, according to the normal procedure, no ketone derivatives were isolated. However, a very definite pink color was obtained on

addition of Schiff's reagent, indicating some form of aldehyde or methyl ketone.

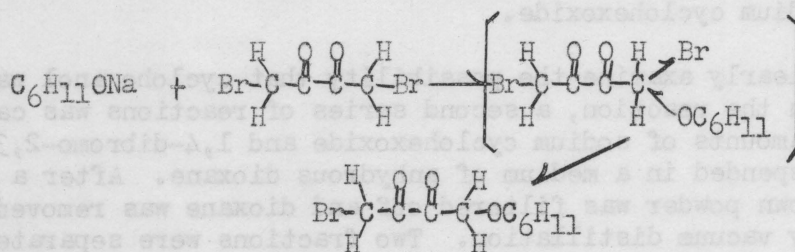
After extraction of the resinous matter with acetone and subsequent evaporation, a brittle, brown mass remained. This resin-like substance contained bromine, as evidenced by the precipitation of silver bromide on addition of silver nitrate to an alcoholic solution.

The brown powder was found to contain sodium and bromine. It was hygroscopic and soluble in water.

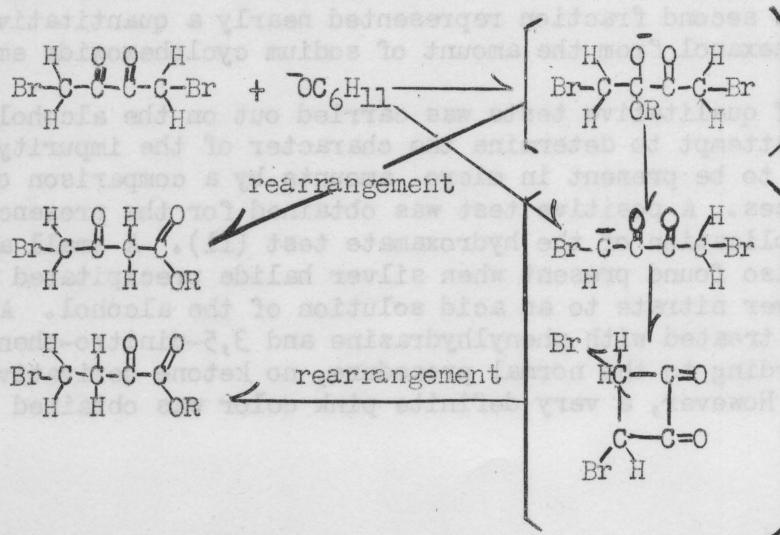
Conclusions

Consideration of possible reaction mechanisms indicated several likely side reactions that might occur. If nucleophilic displacement of bromine, by cyclohexoxide ion, occurs then the desired product should be present, (a). However, due to the presence of a carbonyl group alpha to the bromine, one might expect a molecular rearrangement to occur more readily than the desired displacement, (b). This would lead to the formation of a beta-keto ester which in turn contains an active hydrogen that might be replaced by the sodium ion, releasing cyclohexanol, (c).

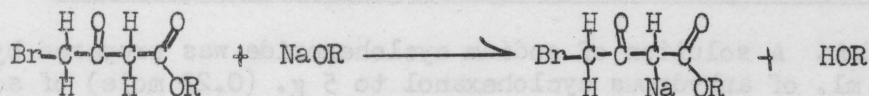
(a)



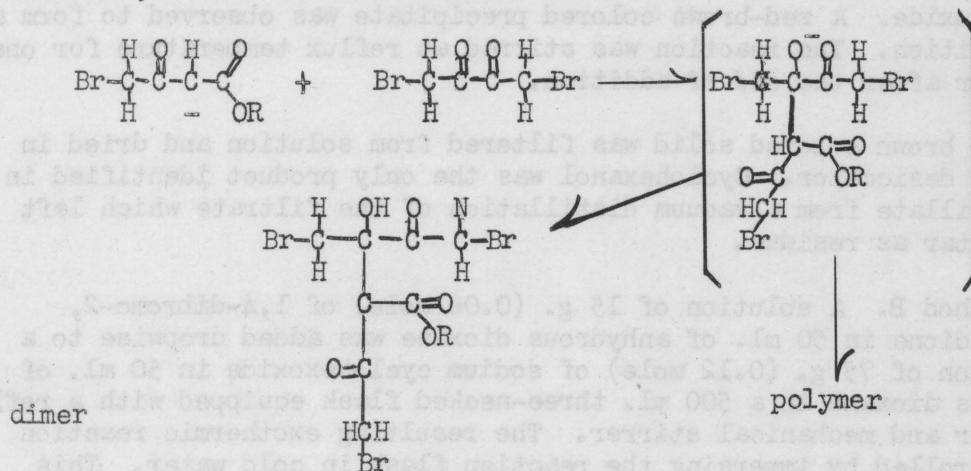
(b)



(c)



Another possibility would be the reaction of an intermediate carbanion to produce a polymer. A number of such possibilities may be postulated, one of which is shown below:



Although the chemistry involved would be of great interest, it was felt that further clarification was unnecessary at the time. From the observation on hand it might be postulated that the formation of polymer and some beta-keto ester does occur, while the greater portion of the product is found as a sodium salt.

That the brittle, halide containing mass might be actually a product of polymerization is further substantiated by several reports in the literature concerning the use of 1,4-dibromo-2,3-butanedione (3, 26). In these instances a brown, amorphous, high molecular weight product was obtained.

Experimental Work

1,4-Dibromo-2,3-butanediol

This compound was prepared by the method of Ruggli, Herzog, Wegmann, and Dahn (42). It involved the direct addition of bromine to 2,3-butanedione in a solution of chloroform.

Attempted preparation of 1,4-Bis-(cyclohexoxy)--2,3-butanedione

Method A. A solution of sodium cyclohexoxide was prepared by adding 150 ml. of anhydrous cyclohexanol to 5 g. (0.22 mole) of sodium in a 500 ml. three-necked flask. The latter was equipped with a mechanical stirrer and dropping-funnel. The alcohol was heated to reflux temperature to insure complete reaction with the sodium. A solution of 25 g. (0.1 mole) of 1,4-dibromo-2,3-butanedione in 180 ml. of anhydrous cyclohexanol was added dropwise to the hot (120° C.) solution of sodium cyclohexoxide. A red-brown colored precipitate was observed to form at each addition. The reaction was stirred at reflux temperature for one half hour after the end of addition.

The brown colored solid was filtered from solution and dried in a vacuum desiccator. Cyclohexanol was the only product identified in the distillate from a vacuum distillation of the filtrate which left a heavy tar as residue.

Method B. A solution of 15 g. (0.06 mole) of 1,4-dibromo-2,3-butanedione in 50 ml. of anhydrous dioxane was added dropwise to a suspension of 75 g. (0.12 mole) of sodium cyclohexoxide in 50 ml. of anhydrous dioxane in a 500 ml. three-necked flask equipped with a reflux condenser and mechanical stirrer. The resulting exothermic reaction was controlled by immersing the reaction flask in cold water. This mixture was stirred for three hours after the addition had been completed.

A brown colored, hygroscopic powder was filtered from the reaction mixture. This solid, when dried in a vacuum desiccator, was a light tan colored powder. A water solution of this powder was found to contain both sodium and bromide ions.

The dioxane was removed from the filtrate by vacuum distillation and a second, higher-boiling fraction was also collected. The residue, a dark colored, brittle mass, was dissolved in acetone and treated with Darco. This acetone solution was allowed to evaporate leaving a dark colored, resinlike material which, from a qualitative test, was found to contain bromine.

The higher-boiling fraction was identified as slightly impure cyclohexanol by a comparison of refractive indices. The volume of alcohol recovered from the distillation represented a nearly quantitative hydrolysis of sodium cyclohexoxide to cyclohexanol. The following data summarizes the observed physical properties of the second fraction as compared to the literature values for pure cyclohexanol.

Boiling point	Observed	Literature
Refractive index	1.4632	1.461
Melting point	16.0° C.	23.9° C.
Boiling point	155.0° C.	160-161° C.
3,5-dinitrobenzoate	108° C. (crude)	113° C. (pure)

The following qualitative tests were made on the impure cyclohexanol in order to obtain some indication of the nature of the impurity.

(1) The ferric hydroxamate test for esters, as given in Cheronis and Entrikan (11), was applied. A dark wine colored solution was observed indicating the presence of an ester group.

(2) Five drops of the alcohol were treated with alcoholic silver nitrate solution. A colloidal suspension of fine white particles was precipitated. On standing and exposure to the sunlight the white colored precipitate turned purple, indicating a reduction of silver halide.

(3) Addition of 2 ml. of Schiff's reagent to 2 drops of the impure alcohol produced a strong pink colored solution. This might indicate the presence of an aldehyde or methyl ketone.

SYNTHESIS OF 2,2'-THENILDIOXIME

Introduction

2,2'-Furildioxime has been applied successfully in the separation of palladous ion from other heavy metals (38). However, some disagreement is found in the literature concerning the value of this dioxime in a quantitative determination of nickel. Soule (47) reported a gravimetric procedure based on the quantitative precipitation of nickel with 2,2'-furildioxime. A more recent investigation (38) reported the composition of the furildioxime to be dependent on the pH of solution from which it is precipitated. Also it was found that 200% excess of reagent was required to give quantitative precipitation of the nickel.

It was felt that an analog of the above dioxime, 2,2'-thenildioxime, might prove to be a more useful analytical reagent.

Discussion of the Methods Investigated

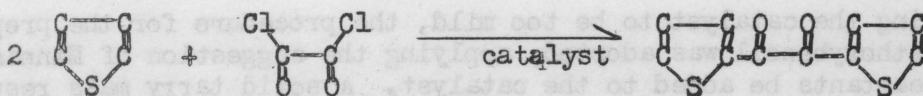
The preparation of 2,2'-thenil might be approached from several starting materials involving a variety of synthetic methods. One of the most common of these methods and the first to be investigated was the benzoin condensation of 2-thiophenealdehyde. This reaction was recently described by Cardon and Lankelma (10) who reported a 32% yield of 2,2'-thenoin. Repeated attempts to effect this condensation failed to produce better than 8% of the pure 2,2'-thenoin.

Several variations of the experimental conditions were employed. The concentration of cyanide and the ratio of the alcohol-water solvent were altered with no apparent effect. In each case the product was kept from crystallizing due to the formation of a red, tarry by-product. When this mixture was treated with Darco, in boiling ethanol, the color was somewhat removed. The red color reappeared, however, on standing for less than twenty-four hours. This was thought to be air oxidation of the crude thenoin, but when the mixture was oxidized by another method only a tar was obtained.

Addition of water to the alcoholic solution, previously treated four successive times with small portions of Darco, caused a separation of the red oil and on standing a yellow, curdy mass developed in the supernatant liquid. This yellow solid proved to be crude 2,2'-thenoin. The crude product was recrystallized from an alcohol-water mixture until a constant melting point of 102-103° was obtained. Here again some disagreement with the literature was observed. Cardon and Lankelma reported a melting point of 107-108° for the pure product after recrystallization from alcohol. The authors also reported a 33% yield of 2,2'-thenil which they obtained by oxidizing the 2,2'-thenoin in a copper sulfate-pyridine mixture.

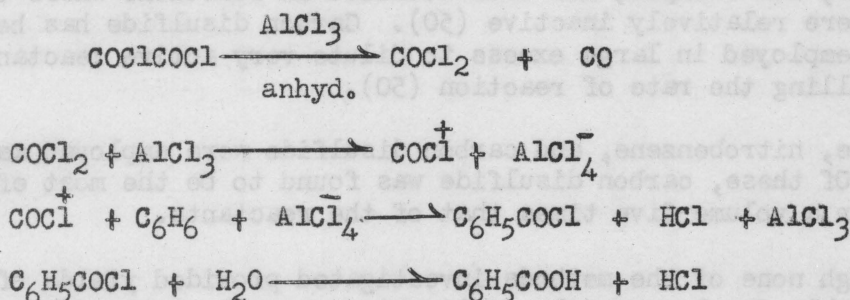
The literature is generous in its description of the oxidation of benzoin compounds to the diketone. A procedure involving the oxidation of benzoin to benzil by the catalytic action of cupric salts was reported as quantitative by Wiess and Appel (55). Their method employed acetic acid as solvent with a small amount of ammonium nitrate to regenerate the catalyst, cupric acetate. A 50% yield of the pure 2,2'-thenil was obtained by this method when the recrystallized 2,2'-thenoin was used. The oxidation of crude thenoin, as mentioned above, resulted in a red tar resembling that obtained in the condensation of 2-thiophene aldehyde.

Due to the overall low yield of 2,2'-thenil by the benzoin condensation, a second method was investigated. It was proposed that the acylation of two moles of thiophene might be effected to yield the desired product by using oxalyl chloride in the presence of a suitable catalyst.



The literature contained several conflicting reports regarding the use of thiophene and oxalyl chloride in the Friedel-Craft synthesis. The acylation of thiophene by acetyl chloride was reported by Stadnikov and Goldfarb (48) resulting in 96% yield of acetothienone when stannic chloride was used as a catalyst. This is in accord with Thomas (50) who stated that the acylation of thiophene is best effected by the presence of a catalyst which is less active than anhydrous aluminum chloride. On the other hand, Minnis (31) reported a 90% yield of phenyl-2-thienyl ketone when a mixture of benzoyl chloride and thiophene were added dropwise into a suspension of anhydrous aluminum chloride in carbon disulfide. This author observed the formation of considerable tar and little product if the anhydrous aluminum chloride was added to the reactants.

The use of oxalyl chloride in Friedel-Crafts reactions has been reported more often as a method of introducing a carboxyl group. This is explained by the action of anhydrous aluminum chloride on oxalyl chloride to produce phosgene and carbon monoxide (50). The phosgene-aluminum chloride complex in turn becomes the reactive reagent that displaces hydrogen. On addition of water the acyl halide is hydrolysed to the acid.



However, 4,4'-diethoxybenzil was recently obtained by the action of oxalyl chloride on phenetole in the presence of anhydrous aluminum chloride (28). In view of these reports a series of reactions were carried out employing several catalysts, reaction media, and a reversal of addition procedures.

Stannic chloride was the first catalyst to be investigated. Thiophene and oxalyl chloride were dissolved in five times their volume of benzene and anhydrous stannic chloride was added dropwise. No evolution of hydrogen chloride was detected even after four hours of reflux.

Assuming the catalyst to be too mild, the procedure for the preparation of 4,4'-diethoxybenzil was adopted, applying the suggestion of Minnis that the reactants be added to the catalyst. A solid tarry mass resulted from this procedure. In repeating the method, exactly as it was described for the 4,4'-diethoxybenzil, a 12% yield of 2,2'-thenil was isolated from the carbon disulfide. Tar was the major product, however. Further modification of this procedure always resulted in some product but a yield of 12% was never again obtained, even when the original conditions were employed.

The same procedure was repeated with anhydrous zirconium tetrachloride in hopes that its catalytic effect would be greater than stannic chloride by less active than aluminum chloride. The evolution of hydrogen chloride was observed after the temperature was increased to 150° C. Further application of heat, until a gentle reflux was obtained, increased the rate of hydrogen chloride evolution but the color of the reaction shifted from yellow to dark brown, as though decomposition was taking place. A 5% yield of 2,2'-thenil was obtained when the reactants were added to the zirconium tetrachloride, suspended in carbon disulfide.

When iodine was employed as a catalyst, only tar was obtained from the reaction mixture.

The solvent medium has been shown to exhibit some effect on the rate of reaction. The solubility of anhydrous aluminum chloride in nitrobenzene, for example, has been utilized in reactions where the reactants were relatively inactive (50). Carbon disulfide has been frequently employed in large excess to dilute very active reactants, thus controlling the rate of reaction (50).

Benzene, nitrobenzene, and carbon disulfide were employed as solvents. Of these, carbon disulfide was found to be the most effective when used in a volume five times that of the reactants.

Although none of the methods investigated provided yields of 2,2'-thenil suitable for large scale application, enough of the diketone was prepared to permit an investigation of the oximation procedure.

The first method to be considered was an adaptation of the procedure described by Reed, Banks and Diehl (37) for the preparation of 2,2'-furildioxime. This method employed the use of a soxhlet extractor and was dependent on the limited solubility of the furil in methanol. The 2,2'-thenil, however, was found to be very soluble in methanol.

The diketone was refluxed in neutral, acidic, and basic methanol solutions of hydroxylammonium chloride. In each case the 2,2'-thenil was recovered and no evidence for the formation of an oxime was found. A white oil was recovered, however, when the reactants were refluxed

in a pyridine-alcohol solution. This product slowly turned pink when allowed to stand in contact with a steel spatula, indicating that perhaps oximation had occurred. An alcohol solution of this oil, when added to a solution of nickel, produced a bright orange colored precipitate. With palladous ion a yellow precipitate was observed.

Although this oil was relatively water insoluble, attempts to obtain a crystalline product from alcohol-water mixtures failed. Steps were taken to remove any remaining pyridine, the presence of which was detected by its characteristic odor. A similar procedure to that for preparing the disodium salt of dimethylglyoxime (44) was used in an effort to purify the oil. The resulting alkaline solution was extracted twice with ether to remove any trace of organic impurity. Neutralization of the alkaline solution, by careful addition of dilute hydrochloric acid and ice, resulted in the formation of a milky liquid. Addition of enough alcohol to clear the solution and subsequent cooling produced a white precipitate. After filtration and drying, this white powder melted over a range of 65-75° C. On remelting the same sample a melting point of 85° C. was observed. Since 2,2'-furildioxime has been reported (37) to crystallize from water as the monohydrate, melting at 84-85° C., it was thought that perhaps the monohydrate of 2,2'-thenildioxime had been obtained.

To eliminate the possibility of a hydrate, the white powder was dissolved in hot benzene. On cooling, clusters of white crystals were obtained, m.p. 114°-130° C. Further recrystallization lowered the melting point range to 95°-110° C. One explanation for the apparent impurity was the possibility that hydrolysis of one of the oxime groups might have occurred in preparing the disodium salt.

It was observed that an alcoholic solution of this product, regardless of the melting point range, would produce a colored precipitate when added to a solution containing nickel or palladium. In the case of nickel, the color of the precipitate varied with the pH of the solution changing from orange to yellow at higher pH levels. Palladium always formed a yellow colored precipitate in acid solution.

Experimental Work

2,2'-Thenoin

The method of Cardon and Lankelma (10) involving the condensation of 2-thiophenealdehyde was used to prepare 2,2'-thenoin. The yield was never greater than 8% of the theoretical, as opposed to a 32% yield claimed by the above workers.

2,2'-Thenil

Method A. A solution of 10 g. (0.04 mole) of crude 2,2'-thenoin, m.p. 85°-95° C., 6 g. of ammonium nitrate and 0.1 g. of cupric acetate in 35 ml. of 80% acetic acid was refluxed for two hours. The 2,2'-thenil separated from the acetic acid solution as fine yellow colored crystals, m.p. 77° C. This crude product was filtered from the solution and the filtrate was diluted with water to precipitate any remaining product. A total of 5 g. of crude 2,2'-thenil was obtained and treated with Darco in boiling methanol. This alcoholic solution was filtered hot and yielded 3 g. of pure 2,2'-thenil, m.p. 79° C., on cooling. This represented a yield of 30% of the pure product.

Method B. A solution of 15.7 ml. (0.2 mole) of thiophene and 8.5 ml. (0.1 mole) of oxalyl chloride in 150 ml. of dry carbon disulfide was placed in a 500 ml. three-necked flask. The latter was equipped with a mechanical stirrer and reflux condenser. The solution was stirred and the temperature was maintained at 0°-2° C. by means of an ice bath. Thirty grams of anhydrous aluminum chloride was added portionwise, with stirring, to the cold carbon disulfide solution over a period of two and one half hours.

The ice bath was removed and the temperature rapidly rose to 30° C. with a vigorous evolution of hydrogen chloride. The contents of the flask solidified as a red colored oily tar. This mixture was warmed gently on a steam bath for one half hour and then cooled in an ice bath. A mixture of 50 ml. of concentrated hydrochloric acid and finely crushed ice was cautiously added to the tarry residue. The temperature rose to 40° C. and a vigorous reaction took place.

The aqueous mixture was transferred to a separatory funnel and the carbon disulfide layer, which was colored dark purple, was separated from the aqueous layer. The carbon disulfide solutions was washed once with a 10% solution of sodium carbonate and twice with water, by shaking in a separatory funnel.

The carbon disulfide was removed by vacuum distillation, leaving a dark brown colored solid as residue. This residue was dissolved in hot glacial acetic acid. The acid solution was decanted from a heavy red colored oil, that had settled to the bottom of the flask, and allowed to cool. Addition of water to the cold, yellow colored acid solution caused the precipitation of a yellow colored amorphous solid. This product was removed from the solution by filtration and treated with Darco in hot methanol. On cooling, 2.6 g. of 2,2'-thenil separated from the alcohol solution, a yield of 12%.

The addition of anhydrous aluminum chloride to the carbon disulfide solution of thiophene and oxalyl chloride at 17° C. resulted in the

formation of a tarry mass before all the aluminum chloride had been added. No product was isolated from this tar.

The addition of a solution of thiophene and oxalyl chloride in 100 ml. of carbon disulfide to a suspension of anhydrous aluminum chloride in carbon disulfide, resulted in the formation of a tar even at 0° C. No product was isolated from this mixture.

Since considerable decomposition was observed in the above procedures, a variety of catalysts, temperature ranges, solvents and methods of addition were employed in an attempt to obtain a greater yield, with less decomposition.

Of the catalysts investigated, none appeared to effective at 0-2° C., on the qualitative basis of the volume of hydrogen chloride that was observed to be evolved during the addition of catalyst. At 10° C. addition of aluminum chloride produced hydrogen chloride at a rate dependent on the rate of addition. Above 10° C. aluminum chloride reacted with decomposition of thiophene to produce a red colored tarry mass.

Addition of zirconium chloride at 20° C. produced a mild evolution of hydrogen chloride and at 40° C. the evolution of hydrogen chloride was more rapid but considerable tar was formed.

Stannic chloride did not produce any reaction at 20° C. or at 80° C. Likewise, iodine was ineffective at the lower temperature but at 80° C. a faint evolution of hydrogen chloride was observed.

Benzene, nitrobenzene, thiophene, and carbon disulfide were employed as solvents. Of these, carbon disulfide was found to be the most suitable solvent, both for the subsequent isolation of the product and as a controlling influence on the more active catalysts. Thiophene was only used as a solvent in the presence of iodine and no reaction was observed.

The method of addition was studied with aluminum chloride and zirconium chloride. From the yield obtained in each case, it appeared that addition of catalyst to reactant was more effective than addition of reactant to catalyst.

The following procedures describe a few of these experimental variations.

Method C. A solution of 15.7 ml (0.2 mole) of thiophene and 8.5 ml. (0.1 mole) of oxalyl chloride in 100 ml. of dry carbon disulfide was added dropwise over a 10 hour period to a suspension of 55 g. (0.23 mole) of anhydrous zirconium chloride in a 500 ml. three-necked flask. The

latter was equipped with a reflux condenser, mechanical stirrer and dropping-funnel. The mixture was stirred at room temperature throughout the addition of the reactants. The zirconium chloride suspension was yellow in color at the start of the reaction but gradually it turned darker and by the completion of the addition of reactants it was a black spongy mass. This mixture was stirred for an additional four hours on a steam bath. On cooling, the carbon disulfide separated as a deep yellow colored layer which was decanted from the spongy mass and treated with a mixture of ice and concentrated hydrochloric acid.

The carbon disulfide layer was washed twice with water before it was vacuum distilled. The residue was taken up in boiling methanol and treated with Darco. This hot alcohol solution was filtered and on cooling 1.1 g. of 2,2'-thenil, a yield of 5%, separated as fine yellow colored crystals.

Method D. A solution of 15.7 ml. (0.2 mole) of thiophene and 8.5 ml. (0.1 mole) of oxalyl chloride in 150 ml. of benzene was treated with 11.5 ml. (0.2 mole) of fuming stannic chloride. The stannic chloride was added dropwise with stirring over a two hour period while the reaction mixture was cooled to 17° C. by a circulating water bath.

A slight change in the color of the solution was observed but no evidence of the evolution of hydrogen chloride was found. A reaction took place with the addition of a mixture of concentrated hydrochloric acid and ice. The benzene layer was separated from the aqueous mixture and dried over calcium chloride. A distillation of the dry benzene solution under a vacuum left only a trace of brown colored powder in the flask. Any thiophene that might have been present as unreacted starting material was probably carried over with the benzene.

Method E. The use of iodine as a catalyst for the acylation of thiophene by acetic anhydride was successful in preparing 2-acetyl thiophene in an 86% yield.

Using 31.4 ml (0.4 mole) of thiophene as solvent and reactant, 8.5 ml. (0.1 mole) of oxalyl chloride and 0.2 g. of iodine were added and the mixture gently refluxed for two hours. No 2,2'-thenil was isolated from this mixture.

2,2'-thenildioxime

A solution of 6 g. (0.09 mole) of hydroxylammonium chloride and 3 g. (0.013 mole) of 2,2'-thenil in 30 ml. of alcohol and 30 ml. of pyridine was placed in a 100-ml. flask equipped with a reflux condenser. The mixture was refluxed for two and one half hours.

The alcohol-pyridine solution was transferred to a beaker and allowed to evaporate by passing a stream of air over the solution. The residue was an oil which would not crystallize on standing in the cold. Furthermore, treatment of this oil with alcohol and Darco was unsuccessful in aiding the crystallization.

The odor of pyridine was still detectable in this oily residue, therefore, it was treated with a 30% solution of sodium hydroxide to form the disodium salt of any dioxime that might be present. This alkaline solution was extracted twice with 20 ml. portions of ether to remove any organic impurities. The aqueous layer was neutralized by the dropwise addition of dilute (6N) hydrochloric acid at 0° C. The addition of acid produced a milky colored liquid. On cooling this liquid in a dry ice-acetone mixture, a white powder was precipitated. This powder was observed to melt over the range of 65°-75° C. Recrystallization of the white powder from benzene raised the melting point range to 114°-130° C., and produced a clear, crystalline compound.

An alcoholic solution of this material, either from the white powder or from the higher melting crystalline material, produced an orange or yellow-orange colored precipitate when added to a solution of nickelous ions. When this alcoholic solution was added to a palladous solution a yellow colored precipitate was formed.

These results might indicate that the lower melting product is a hydrate of the higher melting crystalline material. The fact that a precipitate is obtained with the divalent nickel and palladium ions suggests further that this compound is a dioxime.

Attempted proof of structure of 2,2'-thenildioxime

The remaining portion of the white crystalline material (150 mg.) obtained above, m.p. 114°-130° C., was weighed out as two samples and dissolved in a minimum of alcohol. Two samples were prepared containing known amounts of nickel. The addition of the alcoholic solution to the nickel solution produced a yellow-orange colored precipitate. The pH was adjusted to 7.6 in the first sample and to 8.1 in the second. These solutions were allowed to digest for 12 hours before filtering off the precipitate.

While the precipitate was being dried and weighed, the filtrate was analyzed for nickel by treatment with nioxime. The amount of nickel present in the precipitate was then determined from the difference of the amount found in the filtrate and the known amount that was added originally. Then knowing the weight of the precipitate and the weight of the nickel, in the precipitate, a ratio of the ligand to nickel was calculated, on

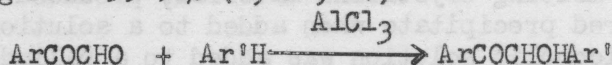
the basis that the organic matter was 2,2'-thienil dioxime. This ratio was found to be 1.63:1 in the precipitate that was formed at a pH of 7.5 and a ratio of 1.36:1 was obtained in the second case where the pH was 8.1.

Since a 2:1 ratio of 2,2'-thienildioxime was not obtained this work cannot be used as a proof of structure or identifying derivative. However, since the ratio of 2,2'-furildioxime to nickel was found to vary with pH it might be expected that the same had occurred in the case of 2,2'-thienildioxime.

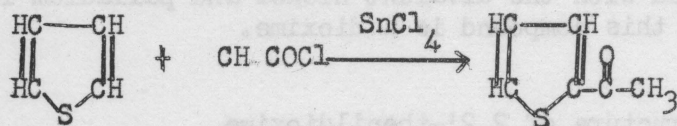
Discussion of Proposed Methods for Future Research

The preparation of 2,2'-thienil, as previously mentioned, might be approached by a number of synthetic methods. The following discussion deals with a few of the methods that have been successfully applied to the preparation of other aromatic or heterocyclic 1,2'-diketones.

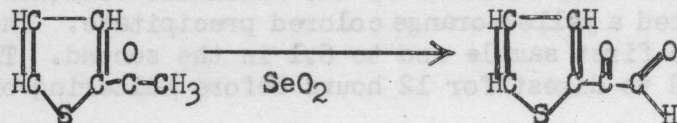
The condensation of arylglyoxals with aromatic hydrocarbons in the presence of aluminum chloride has produced a number of benzoin in yield varying from 35-90% (2, 16, 17).



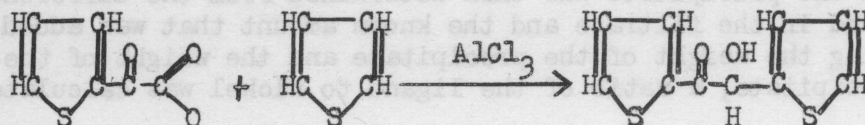
Stadnikov and Goldfarb (48) prepared 2-acetothienone in 96% yield by acylation of thiophene with acetylchloride in the presence of stannic chloride.



Arylglyoxals have been prepared by Riley oxidation of acetophenones (40). By a similar method 2-acetothienone might be converted to thienyl glyoxal.



The thienyl glyoxal might then be condensed with thiophene to give 2,2'-thenoin.



However, due to the action of anhydrous aluminum chloride on thiophene, as was experienced in the acylation of thiophene, another catalyst might be employed to better advantage. Zinc chloride has been reported to be satisfactory in one instance (2).

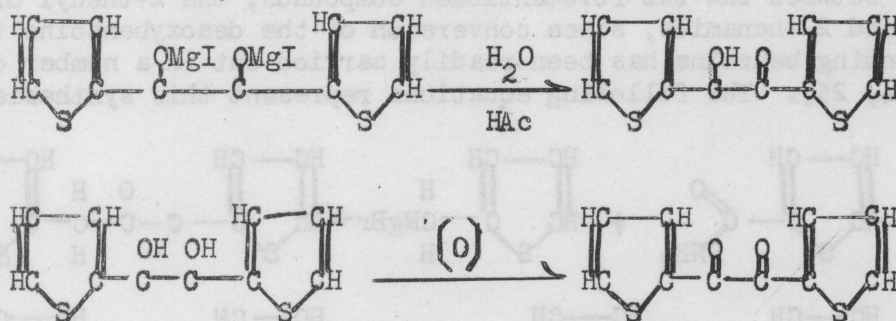
Oxidation of 2,2'-thenoin to 2,2'-thenil has been satisfactorily accomplished, as previously described, by the method of Weiss and Appel (55).

Another method of preparing 2,2'-thenoin, involving the reduction of 2-thenoyl chloride by treatment with magnesium and magnesium iodide in a mixture of ether and benzene as solvents, might be proposed. This method has been used in reducing 2,4,6-trimethylbenzoyl chloride to the corresponding benzoin (18) in a yield of 92%.

2-Thenoyl chloride is commercially available and the following equation represents the postulated reaction.



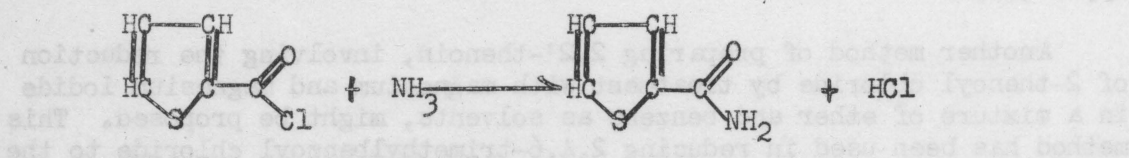
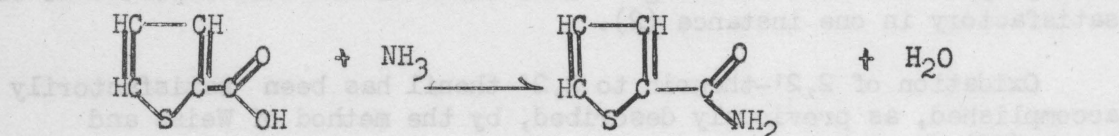
2,2'-Thenoin should result from hydrolysis of the magnesium iodide derivative and oxidation of this product would give 2,2'-thenil.



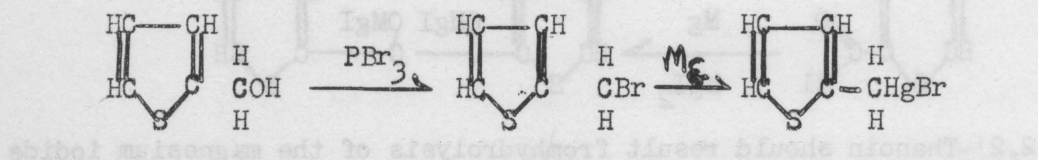
A third synthesis, which is more involved may be proposed on the basis of work reported by Jenkins (24, 25) which deals with the conversion of 2-bromodesoxybenzoins into benzoins in 90% yields.

The preparation of desoxythenoin may be approached by two common methods, (I) from 2-thenamide with a 2-thenyl Grignard reagent, and (II) from 2-thenyl acetyl chloride and thiophene with anhydrous aluminum chloride. Of these, the first would be preferred because of the use of anhydrous aluminum chloride in the second method.

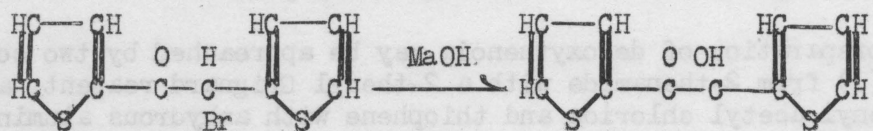
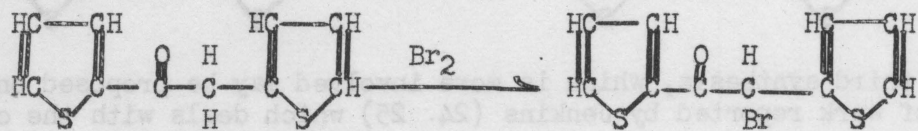
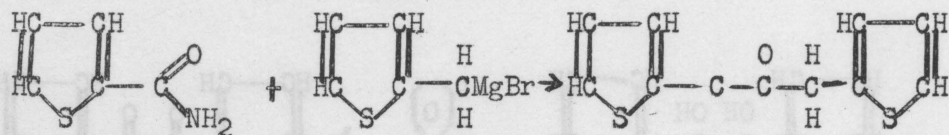
The 2-thenamide might be prepared from 2-thiophene carboxylic acid or from 2-thienoyl chloride as follows:



To prepare a 2-thenyl Grignard reagent, it would be first necessary to prepare 2-thenyl bromide. This compound might be obtained by reduction of 2-thiophenealdehyde to the corresponding alcohol and subsequent replacement of the hydroxyl group with phosphorus tribromide to give 2-thenyl bromide.



The preparation of 2,2'-thenoin probably would depend on the successful reaction between the two forementioned compounds, the 2-thenyl Grignard reagent and 2-thenamide, since conversion of the desoxybenzoins to the corresponding benzoins has been readily carried out in a number of cases (24, 25). The following equations represent this synthesis:



As stated above, the 2,2'-thenoin may be readily oxidized to 2,2'-thenil.

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